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Vulvodynia

Changes in pelvic floor electrical activity and vulvar pain after botulinum toxin treatment of vestibulodynia: are clinical and electrophysiological outcomes related?
Monica Albaladejo-Belmonte, Paula Villa-Munoz, et al.
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https://pubmed.ncbi.nlm.nih.gov/38082636/

Vestibulodynia is a gynecological condition with different treatment options available, including botulinum neurotoxin type A (BoNT/A) injections into the vulvar vestibule. Unlike other treatments, no studies have assessed changes in the myoelectrical activity of the pelvic floor muscles (PFM) after BoNT/A treatment. The aim of this study was thus to evaluate these changes and to correlate them with changes in vulvar pain sensitivity. To do this, 35 patients with vestibulodynia were recruited, the myoelectrical activity of their left and right PFM was recorded with surface electromyography (sEMG), and their vulvar pain sensitivity was monitored according to Visual Analogue Scale (VAS) and an algometer, both before and after BoNT/A treatment. According to our results, patients' signals during PFM relaxation showed a significantly higher power than those of healthy women at baseline, as shown by their root mean square values (RMS), but became similar at follow-up. Patients' mean vulvar pain VAS scores significantly decreased after treatment. Furthermore, baseline-to-follow-up differences of RMS at PFM rest vs. mean VAS were significantly correlated (CC=0.48, $p<0.01$) so that higher reductions in the PFM activity power were associated with higher decreases in vulvar pain.Clinical Relevance- Altered PFM electrophysiological condition of patients with vestibulodynia becomes similar to healthy women's after BoNT/A treatment. This study also points to a relationship between the evolution of clinical and PFM electrophysiological conditions.

Multimodal and Interdisciplinary Interventions for the Treatment of Localized Provoked Vulvodynia: A Scoping Review of the Literature from 2010 to 2023

Alex Rains, Krisztina Bajzak, et al.

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https://pubmed.ncbi.nlm.nih.gov/38250180/

Introduction: Localized provoked vulvodynia (LPV) is a chronic condition characterized by pain in the vulvar vestibule, which can be provoked by pressure or touch and which is not tied to a clear underlying cause. Research into the etiology of and most appropriate treatment strategy for LPV is still limited. **Methods:** Using Arksey and O'Malley's model for scoping reviews, we evaluated the research question: what is the current evidence regarding the efficacy/effectiveness of multimodal or interdisciplinary interventions for the treatment of LPV? We collated and analyzed articles from 2010 to 2023 to capture the current research landscape. **Results:** Our review identified 27 studies, which either compared treatments between classes (eg pharmacologic versus psychologic modalities) or described interdisciplinary treatment programs. We identify several trends in the literature. First, outcome measures are inconsistent between studies, often unvalidated, and may not adequately mirror patient concerns. Second, the absence of appropriate comparator groups in many studies restricts providers' ability to appraise which treatments may be most efficacious. Third, selection bias and demographic homogeneity limit generalizability. Finally, we highlight the need for head-to-head trials of vestibulectomy with other treatments considered first line for vulvodynia management. **Conclusion:** There is insufficient evidence to suggest the superiority of one treatment modality for LPV relative to others or to recommend a particular interdisciplinary management strategy. Future research should use a head-to-head design where sham control is impossible, incorporate patient-centered outcome measures, and investigate impacts of treatment among diverse samples of LPV patients.

Immunohistochemical staining with CD117 and PGP9.5 of excised vestibular tissue from patients with neuroproliferative vestibulodynia

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Background: Neuroproliferative vestibulodynia (NPV), a provoked genital pain characterized by severe allodynia and hyperalgesia, is confirmed in excised vestibular tissue by immunohistochemical staining (>8 CD117-positive immunostained cells/100× microscopic field) rather than by hematoxylin and eosin staining. **Aim:** In this study we sought to assess immunostaining of tissue samples obtained during vestibulectomy surgery and to correlate results with patient outcomes. **Methods:** Patients (n = 65) meeting criteria for NPV who underwent vestibulectomy during the period from June 2019 through December 2022 formed the study cohort. We performed assessment of pathology of vestibular tissues by use of immunohistochemical staining, including quantitation of mast cells by CD117 (mast cell marker) and nerve fibers by protein gene product (PGP) 9.5 (neuronal marker). We analyzed 725 photomicrographs of immunostained tissue sections (100× and 200×) by manual counting and computer-assisted histometry and correlated these data to clinical assessments. **Outcomes:** Outcomes included density of CD117 and PGP9.5 immunostaining in the 1:00-11:00 o'clock and 12:00 o'clock vestibular regions, and patient-reported outcomes assessing sexual function, pain, distress, and

symptom improvement. **Results:** All 65 NPV patients (median age 26 years), 45 with lifelong and 20 with acquired NPV, had severe pain documented by PROs and vulvoscopy and had >8 CD117-immunopositive cells/100× microscopic field. Median cell count values were similar in the 1:00-11:00 o'clock and 12:00 vestibular regions (28.5 and 29.5/100× field, respectively). Likewise, the marker) and nerve fibers by protein gene product (PGP) 9.5 (neuronal marker). We analyzed 725 photomicrographs of immunostained tissue sections (100× and 200×) by manual counting and computer-assisted histometry and correlated these data to clinical assessments. **Clinical Implications:** The pathology of NPV is primarily localized to the vestibular epithelial basement membrane and subepithelial stroma with no visible vulvoscopic findings, making clinical diagnosis challenging. **Strengths and Limitations:** Strengths of this study include the large number of tissues examined with what is to our knowledge the first-ever assessment of the 12:00 vestibule. Major limitations are specimens from a single timepoint within the disease state and lack of control tissues. **Conclusions:** Performing immunohistochemical staining of excised vestibular tissue with CD117 and PGP9.5 led to histometric confirmation of NPV, indications that NPV is a field disease involving all vestibular regions, validation for patients whose pain had been ignored and who had experienced negative psychosocial impact, and appreciation that such staining can advance knowledge.

Immune Dysregulation, Inflammation in Characterizing Women with Vulvodynia, Depression, and Both

Amy Zheng, Bernard L Harlow, et al.

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https://pubmed.ncbi.nlm.nih.gov/38190297/

Background: Depression and vulvodynia are often comorbid. The onset of depression and vulvodynia may be immune and/or stress/environmentally induced. We explored whether vulvodynia, depression, or both occur in response to a Th1-mediated versus Th2-mediated immune response. **Materials and Methods:** We analyzed data from a case-control study of clinically confirmed vulvodynia and history of depression determined through structured clinical interviews. Immune dysregulation and inflammation were categorized based on the following self-reported conditions: rheumatoid arthritis, Sjogren's disease, scleroderma, systemic lupus erythematosus, inflammatory bowel disease, fibromyalgia, osteoarthritis, polycystic ovarian syndrome, diabetes mellitus, uterine fibroids, asthma, atopic dermatitis, and allergic rhinitis. Logistic regression analyses were adjusted for marital status, body mass index, age, and pack years. **Results:** Women with systemic immune dysregulation had higher odds of depression (adjusted odds ratio [aOR] = 1.61, confidence interval [95% CI]: 0.65-3.98), vulvodynia (aOR = 2.45, 95% CI: 1.00-5.96), and comorbid depression and vulvodynia (aOR = 4.93, 95% CI: 2.19-11.10) versus neither condition. Women reporting local immune dysregulation had similar odds of depression (aOR = 1.89, 95% CI: 0.99-3.59), vulvodynia (aOR = 2.12, 95% CI: 1.08-4.18), and comorbid depression and vulvodynia (aOR = 1.96, 95% CI: 0.98-3.90). Women with Th2 inflammation had similar odds of depression (aOR = 2.23, 95% CI: 1.05-4.77) and vulvodynia (aOR = 2.56, 95% CI: 1.20-5.49). Women with Th1 or Th2 inflammation had similar odds of comorbid depression and vulvodynia (aOR = 3.03, 95% CI: 1.48-6.19; aOR = 3.14, 95% CI: 1.49-6.60, respectively). **Conclusions:** Our results suggest that an imbalance of cytokines, indicated by the presence of one or more immune-related health conditions, is associated with an increased risk of vulvodynia and/or depression.

Chronic Pelvic Pain

Effects of Pelvic Floor Muscle Physiotherapy on Urinary, Bowel, and Sexual Functions in Women with Deep Infiltrating Endometriosis: A Randomized Controlled Trial
Simona Del Forno, Laura Cocchi, et al.
Medicina (Kaunas). 2023 Dec 29;60(1):67. doi: 10.3390/medicina60010067.
https://pubmed.ncbi.nlm.nih.gov/38256327/

Background and Objectives: Endometriosis is a chronic and recurrent disease defined as the presence and proliferation of endometrial glands and stroma outside the uterine cavity. It affects up to 6-10% of women of reproductive age and can be classified into superficial, ovarian, and deep infiltrating endometriosis (DIE). Deep infiltrating endometriosis can be associated with pain symptoms and pelvic floor muscle hypertone. Moreover, it may be responsible of bowel, urinary, and sexual dysfunctions with impairment of women's quality of life. Few studies have investigated the role of physiotherapy in women with DIE. Here, we aimed first to evaluate the effects of pelvic floor physiotherapy (PFP) on urinary, bowel, and sexual functions. Secondly, we aimed to evaluate the effects of ultrasound visual feedback during PFP on pelvic floor and subjective modifications in the frequency of sexual intercourse. **Materials and Methods:** This randomized controlled trial was conducted between June 2018 and December 2019 at our tertiary center. Nulliparous women with DIE and superficial dyspareunia were enrolled. At first examination, levator hiatal area (LHA) assessed with 3D/4D transperineal ultrasound, pain symptoms, urinary, bowel, and sexual functions were evaluated. Then, women were randomly assigned to no intervention (control group) or treatment with five individual sessions of PFP (experimental group), and after four months women underwent a second examination. Urinary, bowel, and sexual functions were assessed with validated questionnaires at first and second examinations. In particular, the Bristol Female Lower Urinary Tract Symptoms questionnaire was used to evaluate urinary symptoms, the Knowles-Eccersley-Scott-Symptom questionnaire to assess the presence of constipation, and the Female Sexual Function Index to investigate sexual function. Study outcomes were the comparisons among groups in terms of differences in actual changes in median of questionnaire scores between first and second examinations. **Results:** Thirty women (17 in the experimental group and 13 in the control group) completed the study. No significant differences were found between the two groups regarding urinary, bowel, and sexual functions, although women in the experimental group showed a tendency towards an improvement in constipation symptoms. *Conclusion*: In women with DIE, PFP does not appear to affect urinary, bowel, and sexual functions. Therefore, despite the improvement in superficial dyspareunia, chronic pelvic pain, and PFM relaxation with high treatment satisfaction, women should be informed about the unclear impact of PFP on urinary, bowel, and sexual functions. Larger studies are necessary to further investigate the impact of PFP on these functions.

A Treatment Algorithm for High-Tone Pelvic Floor Dysfunction
Michele Torosis, Erin Carey, et al.
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https://pubmed.ncbi.nlm.nih.gov/38387036/

Objective: To develop evidence- and consensus-based clinical practice guidelines for management of high-tone pelvic floor dysfunction (HTPFD). HTPFD is a neuromuscular disorder of the pelvic floor characterized by non-relaxing pelvic floor muscles, resulting in lower urinary tract and defecatory

symptoms, sexual dysfunction, and pelvic pain. Despite affecting 80% of women with chronic pelvic pain, there are no uniformly accepted guidelines to direct the management of these patients. **Methods:** A Delphi method of consensus development was used, comprising three survey rounds administered anonymously via web-based platform (Qualtrics XM) to national experts in the field of HTPFD recruited through targeted invitation between September and December 2021. Eleven experts participated with backgrounds in urology, urogynecology, minimally invasive gynecology, and pelvic floor physical therapy (PFPT) participated. Panelists were asked to rate their agreement with rated evidence-based statements regarding HTPFD treatment. Statements reaching consensus were used to generate a consensus treatment algorithm. **Results:** A total of 31 statements were reviewed by group members at the first Delphi round with 10 statements reaching consensus. 28 statements were reposed in the second round with 17 reaching consensus. The putative algorithm met clinical consensus in the third round. There was universal agreement for PFPT as first-line treatment for HTPFD. If satisfactory symptom improvement is reached with PFPT, the patient can be discharged with a home exercise program. If no improvement after PFPT, second-line options include trigger or tender point injections, vaginal muscle relaxants, and cognitive behavioral therapy, all of which can also be used in conjunction with PFPT. Onabotulinumtoxin A injections should be used as third line with symptom assessment after 2-4 weeks. There was universal agreement that sacral neuromodulation is fourth-line intervention. The largest identified barrier to care for these patients is access to PFPT. For patients who cannot access PFPT, experts recommend at-home, guided pelvic floor relaxation, self-massage with vaginal wands, and virtual PFPT visits. **Conclusion:** A stepwise approach to the treatment of HTPFD is recommended, with patients often necessitating multiple lines of treatment either sequentially or in conjunction. However, PFPT should be offered first line.

Central Sensitization in Vulvodynia and Endometriosis: What Have We Been Overlooking So Far?
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Obstet Gynecol Surv. 2023 Dec;78(12):745-758. doi: 10.1097/OGX.0000000000001183.
https://pubmed.ncbi.nlm.nih.gov/38134340/

Importance: Women experience more frequent and greater pain than men, although they receive less adequate treatment and are perceived as more anxious than males. Recent clinical research has lead to hypothesize a common etiology for overlapping chronic pain conditions and mood disorders, namely, central sensitization, which originates from an alteration of pain processing pathways in the central nervous system. **Objective:** The aim of this review was to collect all available evidence regarding the potential role of central sensitization in vulvodynia and endometriosis. **Evidence acquisition:** A systematic literature search was performed between July and August 2022 using the electronic database PubMed. The extracted data were summarized using a narrative approach. **Results:** Ten articles were chosen for the review. Participants' mean age was 39.2 years (SD = 5.1). Among serum markers of central sensitization, nitric oxide levels were greater in women with endometriosis than in controls, whereas brain-derived neurotrophic factor and S100B levels differed among pain conditions with structural anomalies and those without. Functional magnetic resonance imaging showed different resting state networks between patients with endometriosis and controls. In neurophysiology studies, cases had reduced pain thresholds, compared with healthy controls. Lastly, self-reported questionnaires suggested a central component of pain in women with endometriosis-related dyspareunia and associated bladder/pelvic floor tenderness. **Conclusions and relevance:** The management of vulvodynia and endometriosis may benefit from a new perspective, which considers their possible central etiology. It is compelling that treatment of pain starts to be considered a therapeutic goal in its own right.

Pelvic Floor Therapy and Initial Interventions for Pelvic Floor Dysfunction in Gynecologic Malignancies
Alice L Ye, Eleanor Johnston, et al.
Curr Oncol Rep. 2024 Jan 31. doi: 10.1007/s11912-024-01498-6.
https://pubmed.ncbi.nlm.nih.gov/38294706/

Purpose of review: This review provides evidence-based updates for the first-line management approaches for pelvic floor disorders in patients with gynecologic malignancies, as well as important provider considerations when referring for pelvic floor physical therapy. **Recent findings:** Currently, there is strong evidence to recommend pelvic floor muscle training as initial treatment for urinary incontinence and for pelvic organ prolapse; some evidence to recommend a more targeted pelvic floor muscle training program for fecal incontinence; and mostly expertise-based evidence to recommend vaginal gels or estrogen to aid with dyspareunia causing sexual dysfunction. More research is greatly needed to understand the role of overactive pelvic floor muscles in survivors with chronic pelvic pain and the treatment of post-radiation pelvic complications such as vaginal stenosis and cystitis. While pelvic floor disorders are common concerns in gynecologic cancer survivors, there are evidence-based initial noninvasive treatment approaches that can provide relief for many individuals.

Coping Strategies with Genito-Pelvic Pain/Penetration Disorder: A Qualitative Study
Mojdeh Banaei, Vahid Mehrnoush, et al.
Pain Res Manag. 2023 Dec 16:2023:5791751. doi: 10.1155/2023/5791751. eCollection 2023.
https://pubmed.ncbi.nlm.nih.gov/38144227/

Background: Genital/pelvic pain penetration disorder (GPPPD) decreased mental and physical functioning, reduced quality of life, and reduced feelings of inadequacy and worthlessness, all of which impair the ability of women with GPPPD to enjoy sex. This qualitative study was conducted to identify which factors can reduce sexual stress and help Iranian women cope with GPPPD. **Methods:** This qualitative study was conducted through the participation of 18 women with GPPPD diagnosed by a sexologist and using DSM-IV diagnostic criteria from March to July 2022, Iran. The samples were selected using the purposive sampling method and considering the maximum variation. The semistructured question guide was used as a data collection tool and data collection continued until data saturation was reached. The collected data were analyzed using conventional content analysis approach. **Results:** Data analysis led to the emergence of three main themes: "problem-focused coping" which included the three categories of received social support, problem self-control, and penetration replacement; "emotion-focused coping" which included three categories: a couple's negative reaction to the problem, attachment disorder, and surrendering the problem; and "treatment-seeking" which consisted of searching and choosing a therapist to solve the problem, ineffective medical approaches, and ineffective nonmedical approaches. **Conclusion:** Coping strategies in women with GPPPD were classified as "problem-focused coping," "emotion-focused coping," and "treatment-seeking." These findings indicate a need for GPPPD information and education, as well as a need for healthcare professionals to actively inquire about sexual problems and commit to serious treatment efforts. Cultural interventions that promote sexual pleasure can aid in the management of GPPPD.

Investigating the role of the pelvic floor muscles in sexual function and sexual response: a systematic review and meta-analysis

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https://pubmed.ncbi.nlm.nih.gov/38303662/

Introduction: The pelvic floor muscles (PFMs) have been suggested to play a key role in sexual function and response in women. However, syntheses of the evidence thus far have been limited to interventional studies in women with pelvic pain or pelvic floor disorders, and these studies have failed to fully capture the involvement of the PFMs in a broader population. **Aim:** We sought to appraise the evidence regarding the role of the PFMs in sexual function/response in women without pelvic pain or pelvic floor disorders. More specifically, we examined the following: (1) effects of treatment modalities targeting the PFMs on sexual function/response, (2) associations between PFM function and sexual function/response, and (3) differences in PFM function between women with and those without sexual dysfunction. **Methods:** We searched for all available studies in eight electronic databases. We included interventional studies evaluating the effects of PFM modalities on sexual outcomes, as well as observational studies investigating the association between PFM function and sexual outcomes or the differences in PFM function in women with and those without sexual dysfunction. The quality of each study was assessed using the Mixed Methods Appraisal Tool. Estimates were pooled using random-effects meta-analyses whenever possible, or a narrative synthesis of the results was provided. **Main outcomes:** The main outcomes were sexual function (based on a questionnaire)/sexual response (based on physiological test), and PFM function (assessment of the PFM parameters such as strength and tone based on various methods). **Results:** A total of 33 studies were selected, including 14 interventional and 19 observational studies, most of which (31/33) were deemed of moderate or high quality. Ten out of 14 interventional studies in women with and without sexual dysfunctions showed that PFM modalities had a significant effect on sexual function. Regarding the observational studies, a meta-analysis revealed a significant moderate association between PFM strength and sexual function (r = 0.41; 95% CI, 0.08-066). Of the 7 observational studies performed to assess sexual response, all showed that the PFMs were involved in arousal or orgasm. Conflicting results were found in the 3 studies that evaluated differences in PFM function in women with and those without sexual dysfunction. **Clinical implications:** Our results highlight the contribution of the PFMs in sexual function/response. **Strengths and limitations:** One strength of this review is the inclusion of a broad range of study designs and outcomes, allowing a thorough synthesis of evidence. However, interpretations of these data should consider risk of bias in the studies, small sample sizes, and the absence of control/comparison groups. **Conclusion:** The findings of this review support the involvement of the PFMs in sexual function/response in women without pelvic pain or pelvic dysfunction. Well-designed studies should be performed to further investigate PFM modalities as part of the management of sexual dysfunction.

Botulinum toxin injection in vulva and vagina. Evidence from a literature systematic review

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https://pubmed.ncbi.nlm.nih.gov/38353087/

Introduction: Botulinum toxin (BoNT) administration has been proposed in the gynecologic field for pelvic, vulvar and vaginal disorders. On this regard, we aimed assessing the therapeutic effectiveness and safety of BoNT usage in the treatment of vaginal, vulvar and pelvic pain disorders. **Methods:** We

searched for all the original articles without date restriction until 31.12.2021. We included all the original articles which administered botulinum toxin in the vulva or vagina of women suffering from vaginismus, dyspareunia, and chronic pelvic pain. Only English language studies and those performed in humans were eligible. We excluded all case reports and pilot study from the qualitative analysis, although we accurately evaluated them. 22 original studies were finally included in the systematic review. **Results:** Botulinum toxin injection was found to be effective in improving vulvar and vaginal dyspareunia, vaginismus, and chronic pelvic pain. No irreversible side effects were detected. Major side effects reported were transient urinary or fecal incontinence, constipation and rectal pain. The risk of bias assessment proved original articles to be of medium quality. No metanalysis could have been performed since lack of congruency in the definition of pathology and methods of botulinum toxin administration. **Conclusion:** Data extraction pointed out different endpoints and different methods of analysis. Studies focus on different types of participants and use various techniques and timing. According to the best evidence available, different techniques provide evidence about positive outcomes, with the need for a standardized protocol.

Using Myofascial Therapy to Improve Psychological Outcomes, Quality of Life, and Sexual Function in Women with Chronic Pelvic Pain-A Case Series
Esther Diaz-Mohedo, Fidel Hita-Contreras, et al.
Healthcare (Basel). 2024 Jan 24;12(3):304. doi: 10.3390/healthcare12030304.
https://pubmed.ncbi.nlm.nih.gov/38338190/

(1) Background: Chronic pelvic pain represents a prevalent condition afflicting women. Research has highlighted the presence of psychological distress and sexual dysfunction in these individuals. Regrettably, myofascial pelvic pain often goes unnoticed and untreated despite its integral role in chronic pelvic pain. (2) Methods: By employing a longitudinal case series design, we studied eighteen women afflicted with chronic pelvic pain. Over a 12-week period, these participants underwent 15 sessions of myofascial therapy. Data encompassing sociodemographic particulars, the Hospital Anxiety and Depression Scale, the Medical Outcomes Study Short Form 12 questionnaire, and the Female Sexual Function Index were collected at baseline, 12 weeks post-intervention, and again at the 24-week mark. (3) Results: After a span of 12 weeks subsequent to the intervention, the participants demonstrated noteworthy enhancements ($p < 0.001$) in their depression and anxiety scores, their overall Mental Component scores in the Medical Outcomes Study Short Form 12, as well as sexual function. Importantly, these gains were sustained at the 24-week juncture post-therapy. (4) Conclusions: The findings stemming from our prospective case study underscore the potential utility of myofascial therapy for women grappling with chronic pelvic pain. This form of intervention yields significant advancements in alleviating anxiety, depression, health-related quality of life, and sexual function.

Genitourinary Syndrome of Menopause/Vulvovaginal Atrophy

Women with Genitourinary Syndrome of Menopause Treated with Vaginal Estriol, Microablative Fractional CO_2 Laser and Microablative Fractional Radiofrequency: A Randomized Pilot Study
Carla Dias de Oliveira, Ana Maria Homem de Mello Bianchi, et al.
Photobiomodul Photomed Laser Surg. 2023 Dec;41(12):718-724. doi: 10.1089/photob.2023.0113.
https://pubmed.ncbi.nlm.nih.gov/38085184/

Objective: This pilot study intended to assess the feasibility of a large-scale randomized clinical trial designed to analyze the effectiveness of microablative fractional CO_2 laser (CO_2L) and microablative fractional radiofrequency (RF) compared with vaginal estriol (VE) as treatments for women with moderate-to-severe Genitourinary Syndrome of Menopause (GSM). **Methods:** Participants were randomized into VE, CO_2L, or RF groups. In the VE group, women were required to use vaginal estriol cream for 14 days and then twice a week for 4 months. In the CO_2L and RF groups, three energy therapies were administered at monthly intervals. Visual Analog Scale (VAS) for GSM symptoms, Female Sexual Function Index (FSF-I), Vaginal Health Index (VHI), and Nugent Score (NS) were analyzed before and 120 days after the beginning of the treatments. Pain scores were verified after each CO_2L and RF session. **Results:** Thirty-four participants completed the study: 11 in the VE group, 11 in the CO_2L group, and 12 in the RF group. No unexpected or serious adverse events were observed. We also verified that GSM symptoms, sexual function, and VHI significantly improved ($p < 0.05$) with no difference among the groups. NS did not show statistically significant difference before and after the treatments. Pain during RF application was associated with higher scores. **Conclusions:** The study is feasible and does not seem to have safety implications. Preliminary results suggest that CO_2L and RF are good alternatives to VE for ameliorating clinical symptoms, FSF-I, and VHI in patients with GSM. Clinical Trial Registration number: NCT04045379.

Fractional CO_2 Laser, Radiofrequency and Topical Estrogen for Treating Genitourinary Syndrome of Menopause: A Pilot Study Evaluating the Vulvar Vestibule

Madalena Leonor Pereira Campos, Ana Maria Homem Mello Bianchi-Ferraro, et al.
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https://pubmed.ncbi.nlm.nih.gov/38256341/

Background and Objectives: Genitourinary syndrome of menopause (GSM) affects more than half of postmenopausal women. This study aimed to evaluate the clinical and histological aspects of microablative fractionated CO_2 laser (CO_2L), microablative fractionated radiofrequency (RF) and intravaginal estrogen (ET) therapy as GSM treatments for the vulvar vestibule. Materials and Methods: This study included postmenopausal women with at least one moderate-to-severe complaint of GSM. Women in the CO_2L and RF groups received three monthly sessions of outpatient vulvovaginal therapy. The procedures were performed 30 min after applying 4% lidocaine gel to the vulva and vaginal introitus. Vulvar vestibular pain was assessed after each application using a 10-point VAS. A follow-up evaluation was performed 120 days after beginning each treatment. Digital images of the vulva were obtained and a 5-point Likert scale (1 = much worse, 2 = worse, 3 = neutral, 4 = better, 5 = much better) was used to assess the global post-treatment women's impression of improvement regarding GSM. Results: A significant change in clinical aspects of the vulva was observed after all treatments with a reduction in the atrophic global vulvar aspect and an enhancement of the trophic aspect. High satisfaction was also reported after treatment according to the Likert scale evaluation: CO_2L (4.55 ± 0.97), RF (4.54 ± 0.95), CT (4 ± 1.41), $p = 0.066$. Histological evaluation revealed enhanced dermal papillae before pre-treatment, significantly reducing post-treatment in all groups ($p = 0.002$). No unintended effects were reported. Conclusions: CO_2L, RF, and ET significantly improved GSM concerning the vulvar vestibule at the 4 months follow-up.

Safety and efficacy of non-ablative CO_2 laser treatment of vulvo-vaginal atrophy in women with history of breast cancer

Alessandra Lami, Stefania Alvisi, Maurizio Baldassarre, et al.

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https://pubmed.ncbi.nlm.nih.gov/38253692/

Purpose: Breast cancer survivors (BCS) suffer severe vulvo-vaginal atrophy (VVA) and some of the most effective therapies are contraindicated. In literature we have no data about the non-ablative CO_2 laser on these women. The aim of this study was to examine its efficacy, safety and acceptability in BCS. **Materials and methods:** The enrolled women underwent 3 sessions of laser therapy (t0, t1, t2) and a one-month follow up examination (t3). At each time point we measured objective signs of VVA via VHI (Vaginal Health Index) and VuHI (Vulvar Health Index) and subjective parameters (Dryness, Burning, Itching, Dysuria) via visual analog scales (VAS). In sexually active women we evaluated the sexual function with FSFI (Female Sexual Function Index), FSDS (Female Sexual Distress Score) scores and MENQOL (menopause quality of life questionnaire). **Results:** We enrolled 26 BCS. The mean VHI, VuVHI, dryness and burning VAS scores improved significantly and this improvement was not influenced by the initial VVA grade. MENQOL sexual domain, Lubrication, Orgasm and Pain domains and FSFI total score improved significantly, while Desire, Arousal and Satisfaction domains of FSFI and FSDS did not. At t0 women using Aromatase Inhibitors suffered more severe vaginal dryness than women using Tamoxifen or no therapy, but the three subgroups improved without differences. No adverse event and minimum discomfort were reported. **Conclusions:** The non-ablative CO_2 laser is a safe and effective treatment of VVA and has positive effects on sexual function in BCS regardless the use of adjuvant therapies and the initial grade of VVA.

CO_2 Laser versus Sham Control for the Management of Genitourinary Syndrome of Menopause: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Anastasia Prodromidou, Dimitrios Zacharakis, et al.

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https://pubmed.ncbi.nlm.nih.gov/38138921/

In the context of the menopausal transition, genitourinary syndrome of menopause (GSM) refers to a range of genitourinary symptoms, from vaginal dryness to dysuria and urinary urgency. While hormonal treatments are standard, their associated side effects have driven the exploration of alternatives like vaginal CO_2 laser. We aimed to evaluate the randomized controlled trials (RCTs) comparing vaginal CO_2 laser treatment for GSM to sham controls. This systematic review sourced four electronic databases until June 2023. The analysis incorporated seven RCTs with 407 women. The CO_2 laser and sham control were comparable for most parameters, including the female sexual function index (FSFI) and visual analogue scale (VAS) for dyspareunia, vaginal health index, pH, and patient satisfaction. However, the CO_2 laser group showed significant improvement in the vaginal assessment scale for GSM symptoms. Sensitivity analyses revealed that parameters like FSFI showed significant differences in favor of CO_2 laser group upon the exclusion of specific studies. In conclusion, vaginal CO_2 laser therapy emerges as a promising alternative for GSM management, especially for most bothersome GSM symptoms; however, the need for further well-designed RCTs remains to validate its broad safety and efficacy.

Real-world performance and safety of vaginal ovules in reducing the vaginal symptoms associated with vulvovaginal atrophy and postmenopausal sexual dysfunction
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Decreasing estrogen levels during the postmenopausal period results in tissue atrophy and physiological changes, such as thinning of the vaginal epithelium, prolapse and decreased pelvic floor strength and control. Sexual dysfunction associated with vaginal dryness occurs in postmenopausal patients. The present study (trial no. NCT05654610) was designed as an observational, multicenter, real-world clinical investigation to evaluate the performance and safety of the medical device Halova® ovules in decreasing vaginal symptoms associated with vulvovaginal atrophy and sexual dysfunction. A total of 249 female participants were treated with Halova ovules, both in monotherapy and in combination with vaginal lubricants. The primary objective was to evaluate the tolerability of Halova ovules in the management of symptoms associated with perimenopause or genitourinary syndrome of menopause. The evolution of clinical manifestations such as vaginal dryness, dysuria, dyspareunia and endometrial thickness was defined a secondary objective. Halova ovules were rated with 'excellent' clinical performance by 92.74% of participants as a standalone treatment and 95.71% of the study participants when used in association with vaginal lubricants. Sexual dysfunction-associated parameters, such as vaginal dryness and dyspareunia, were reduced by similar percentages in each arm, 82% (monotherapy) and 80% (polytherapy) for vaginal dryness and 72% in monotherapy vs. 48% polytherapy reducing dyspareunia. No adverse reactions associated with treatment with Halova were reported. The medical device demonstrated anti-atrophic activity in the genitourinary tract, resulting in significantly improved symptoms associated with normal sexual functioning.

Sexual Dysfunction and Dyspareunia in the Setting of the Genitourinary Syndrome of Menopause
Neha G Gaddam, Sheryl A Kingsberg, et al.
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Sexual dysfunction is a common consequence of the genitourinary syndrome of menopause (GSM). In this book chapter, we discuss the pathophysiology, prevalence, evaluation, and evidence-based management of sexual dysfunction in patients affected by GSM. Additionally, we present an algorithm to guide clinicians in the management and treatment of sexual dysfunction in this setting based on available evidence and best practices.

Persistent Genital Arousal Disorder

Clinical characterisation of women with persistent genital arousal disorder: the iPGAD-study
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Persistent Genital Arousal Disorder (PGAD) is a rare condition-mostly in women-where patients perceive prolonged genital arousal without any sexual desire or stimulation. Etiopathological considerations

reach from peripheral to central issues over local disturbance of the pudendal nerve to neuropathy, psychosocial, and pharmacological theories. Since well controlled clinical studies about PGAD in conjunction with a mental and somatic health status are missing, this study is a detailed clinical investigation of PGAD patients compared to healthy controls. 26 women who fulfilled diagnostic criteria for PGAD were compared to 26 age matched healthy controls. Investigations included comparison of vegetative, gynaecological and sexual history, psychiatric features as well as a (neuro-)radiological, neurophysiological and gynaecological examination. Moreover, a detailed clinical characterisation of PGAD symptoms was performed. PGAD symptoms were mostly characterised as tingling or prickling and were permanently present. In over 80%, PGAD symptoms were located in the clitoris. Almost 70% reported radiations to other regions of the body. Most frequent trigger factors were tight clothes, mental stress, driving a car/bus/bicycle and sexual intercourse. Relieving factors were mainly distraction, relaxation, physical exercise, masturbation and swimming. In group comparisons, PGAD presented with significant higher rates of sexual dysfunctions, spontaneous orgasms, swelling of the genitals, extraordinary lubrication as well as higher rates in depression, agoraphobia, generalized anxiety disorder and lifetime panic disorder. Significantly more PGAD patients were diagnosed with restless legs symptoms. In contrast childhood traumatization, somatization disorder, suicidality, gynaecological as well as neurophysiological examination of the pudendal nerve were not different between the groups. MRI of the brain, pelvis and spinal cord was unsuspicious and incidental findings - including Tarlov cysts or pelvic venous congestion - were equally distributed among the groups. In summary, our study provides a careful characterization of women with PGAD highlighting a serious mental burden, most probably as a consequence of PGAD. With the current set of clinical investigations there was no evidence of a clear causal relationship to a specific clinical finding as it has been previously discussed. Future studies and additional techniques will have to further explore where and how in the peripheral or central nervous systems PGAD develops.

Effectiveness of Brexpiprazole in a Patient With Bipolar Disorder and Comorbid Persistent Genital Arousal Disorder/Genito-Pelvic Dysesthesia: A Case Report

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Although the symptoms of persistent genital arousal disorder/genito-pelvic dysesthesia (PGAD/GPD) can have negative impacts on patients' lives, it is an under-recognized clinical entity. We describe the case of a 61-year-old Japanese female who suffered simultaneously from bipolar disorder and PGAD/GPD. She developed PGAD/GPD approx. 10 years after being diagnosed with bipolar disorder. Despite 20 years of various drug treatments, her bipolar disorder and PGAD/GPD symptoms showed little improvement. She had also undergone multiple sessions of cognitive behavioral therapy (CBT) and mindfulness, nerve block, botulinum toxin injections, and laser treatment for PGAD/GPD. Her PGAD/GPD symptoms remained with no significant improvement, and her bipolar disorder symptoms had also not responded well to medication. With the administration of brexpiprazole, she achieved remission of her bipolar disorder. Her PGAD/GPD symptoms also eventually improved. When PGAD/GPD is comorbid with bipolar disorder, the improvement of bipolar disorder may also lead to relief of PGAD/GPD symptoms. This case reveals that brexpiprazole, which has a unique profile, may be effective for PGAD/GPD.

Pudendal Neuralgia

[Efficacy and safety of different nerve block methods for the treatment of pudendal neuralgia]
[Article in Chinese]
C Wang, J J Niu, et al.
Zhonghua Yi Xue Za Zhi. 2024 Jan 2;104(1):52-56. doi: 10.3760/cma.j.cn112137-20230927-00592.
https://pubmed.ncbi.nlm.nih.gov/38178768/

Objective: To identify efficacy and safety of pudendal nerve block in tubing through the third posterior sacral foramen for the treatment of pudendal neuralgia (PN). **Methods:** A retrospective study with 222 PN patients was conducted in the Department of Pain Management of Beijing Tsinghua Changgung Hospital from January 2020 to April 2023. These patients were divided into two groups based on their treatment methods: pudendal nerve block in tubing through the third posterior sacral foramen (observation group, *n*=101) and ultrasound-guided pudendal nerve block (control group, *n*=121). Primary outcome measure was the 90-day postoperative pain relief rate. Secondary outcome measures included visual analog scale (VAS) at 1, 7, 14, 30 and 90 d after surgery, the incidence of tramadol uses after surgery, postoperative self-rating anxiety scale (SAS) scores and the incidence of adverse events. Factors that influenced pain relief within 90 days after surgery were analyzed by using binary logistic regression analysis. **Results:** Observation group included 34 males and 67 females, aged (49.8±16.0) years old. Control group included 38 males and 83 females, aged (43.7±14.0) years old. The 90-day postoperative pain relief rate of the observation group patients was 38.6% (39/101), which was higher than the 24.0% (29/121) of the control group patients (*P*=0.018). Both the observation group and the control group showed an interaction effect of time and group after treatment for VAS scores (both *P*<0.05). In intra-group comparison, the VAS scores at 1, 7, 14, 30 and 90 d after treatment in both groups were lower than those before treatment (all *P*<0.05). In inter-group comparison, the differences of the VAS scores were not statistically significant in the observation group compared with those in the control group at 1, 7, 14, 30 and 90 d after surgery (all *P*>0.05). The SAS score of the observation group at 90 d after surgery was 51.5±6.2, which was lower than the 53.4±5.8 of the control group (*P*=0.022). There was no statistically significant difference in the incidence of postoperative tramadol uses and adverse events between the two groups (both *P*>0.05). Pudendal nerve block in tubing through the third posterior sacral foramen was a protective factor for pain postoperative relief in PN patients at 90 d after surgery (*OR*=1.92, 95%*CI*: 1.05-3.48, *P*=0.033). **Conclusion:** Pudendal nerve block in tubing through the third posterior sacral foramen is a safe and effective minimally invasive treatment. It has a higher postoperative pain relief rate within 90 d after surgery, without increasing the uses of postoperative rescue analgesics and the incidence of adverse events.

Dermatological Conditions

The efficacy of 5-aminolevulinic acid photodynamic therapy for pediatric vulvar lichen sclerosus
Shan Zhang, Yukun Wang, et al.
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Background: Prepubertal girls are one of the vulnerable populations of vulvar lichen sclerosus (VLS), which results in a decreased quality of life and increases risk of vulvar cancer. But the therapeutic effects

of traditional topical remedies are unsatisfactory in some pediatric patients. 5-Aminolevulinic acid photodynamic therapy (ALA-PDT) is an effective treatment for refractory VLS patients, but no study has been conducted in child patients. **Methods:** The patients included in this study underwent three sessions of ALA-PDT at 2-week intervals. All patients were evaluated for objective clinical appearances and subjective symptoms quantitatively. Statistical analysis comparing parameters at baseline and after three-time ALA-PDT was performed. **Results:** A total of seven VLS girl patients were included in this study. Both primary objective appearances (lesion size and depigmentation) and subjective symptoms (itching and burning pain) were improved remarkably after the third treatment. Besides, adverse effects, mainly as pain and post-treatment edema, were mild and could be tolerated. **Conclusions:** ALA-PDT is an effective and safe therapeutic option for VLS girl patients. Compared with adult patients, the symptoms resolved more quickly in child patients.

Searching for a "window of opportunity" in the treatment of vulvar lichen sclerosus: evidence for therapeutic benefits of an early corticosteroid treatment
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Background: Vulvar lichen sclerosus (VLS) is characterized by progressive anatomical changes which become increasingly severe and irreversible. **Objectives:** To investigate if a "window of opportunity" exists in VLS, i.e. to assess if an early treatment may prevent disease progression and facilitate clearance of symptoms and/or signs. Methods This retrospective, cohort study included VLS patients treated for the first time with a topical corticosteroid, namely with mometasone furoate 0.1% ointment, for 12 weeks (2016-2021). Scoring of subjective symptoms (global subjective score, GSS, and dyspareunia) and clinical features (global objective score, GOS, and sclerosis-scarring-atrophy) was performed at baseline (T0) and at the control visit (T1). We assessed if the achievement of clearance in GSS, GOS, sclerosis-scarring-atrophy or dyspareunia depended on the time elapsed between VLS onset and treatment initiation. **Results:** Among the 169 patients (59.2±13.2 years) included, the median time between VLS onset and first treatment was 14.0 months. At T1, 48.8% of patients achieved clearance of GSS, 28% of GOS and 11.9% of both GSS and GOS, 57.9% of dyspareunia and 23.1% of sclerosis-scarring-atrophy. Logistic regression model showed that each 10-month increase in treatment initiation adversely affected the clearance of GSS and starting treatment within 6 months of disease onset was significantly associated with clearance of GOS and sclerosis-scarring-atrophy. **Conclusion:** Early treatment is crucial in determining a complete healing of VLS-related symptoms and signs, especially of tissue sclerosis-scarring-atrophy, that appear poorly responsive, or even unresponsive, after the earliest stages of the disease. Thus, our findings provide evidence for a 'window of opportunity' in VLS treatment.

Lichen planus is associated with other autoimmune conditions: A retrospective population-level study
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To the Editor: Lichen planus (LP) is a T-cell mediated chronic inflammatory skin disease that affects mucocutaneous surfaces. LP has been associated with autoimmune conditions like alopecia areata, autoimmune thyroiditis, celiac disease, dermatomyositis (DM), type 1 diabetes mellitus, Sjogren's syndrome, and systemic lupus erythematosus. We performed a population-level retrospective study

using extensive data from numerous health care organizations throughout the US to explore whether additional autoimmune conditions are associated with LP and confirm previously found associations.

We utilized TriNetX, a global health research network, to retrospectively generate a patient cohort from the US Collaborative Network. Our study included data between June 2003 and 2023 of over 95 million patients from 57 US health care organizations. International Classification of Diseases-10 (ICD-10) code L43 was used for LP and L20.9 was used for atopic dermatitis (AD). AD was used as the control cohort. Patients with LP were excluded from the control cohort. Diagnoses prior to ICD-10 codes were mapped by TriNetX using General Equivalence Mappings. The cohorts were 1:1 propensity score matched by age, sex, and race/ethnicity. We then utilized ICD-10 codes to identify patients who were diagnosed with autoimmune conditions following a diagnosis of LP. Odds ratios and 95% confidence intervals were utilized to identify associations between LP and other conditions.

We identified 77,060 LP patients and an equal number of matched controls (Table I). Patients with LP had increased odds of: alopecia areata, autoimmune thyroiditis, DM, discoid lupus erythematosus, lichen sclerosus (LS), morphea, other local lupus erythematosus, primary biliary cirrhosis, Sjogren's syndrome, subacute cutaneous lupus erythematosus, systemic lupus erythematosus, systemic sclerosis, and vitiligo. Patients with LP had decreased odds of inflammatory arthritis, rheumatoid arthritis, multiple sclerosis, psoriasis, type 1 diabetes mellitus, and vitamin D deficiency. We found no association between LP and celiac disease, Crohn's disease, myasthenia gravis, psoriatic arthritis, reactive arthritis, or ulcerative colitis (Table II).

Treatment of erosive vulvovaginal lichen planus with tofacitinib: A case series

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Lichen planus (LP) is a chronic inflammatory skin disease that affects cutaneous and mucosal sites and is often recalcitrant to topical therapies. Erosive lichen planus (ELP) is a severe variant which is often less responsive to therapy. ELP tends to occur on the oral and anogenital mucosa and modified mucous membranes but can also involve other mucosal sites, such as the esophagus. ELP significantly affects quality of life (QOL) and if left untreated, can lead to chronic scarring. Erosive vulvovaginal LP (EVVLP) can lead to narrowing of the introitus and midline fusion, resulting in pain, itch, irritation, dyspareunia, dysuria, and recurrent urinary tract infections due to urinary retention and obstruction.
Topical immunosuppression with corticosteroids or calcineurin inhibitors are usually considered first-line for EVVLP, while resistant disease may be treated with intralesional, oral, or intramuscular steroids.[2] Studies have estimated that up to 40% of women with EVVLP do not respond to first-line topical steroid therapy and require systemic agents. Steroid-sparing agents such as methotrexate, mycophenolate mofetil, hydroxychloroquine, and rituximab have been used with varying levels of efficacy. Thus, there is significant need for more efficacious treatments, such as molecularly-targeted therapies for EVVLP.

While the pathogenesis of ELP is not completely understood, cytokines in the Janus kinase – signal transducer and activator of transcription (JAK-STAT) signaling pathway are thought to play a role in disease development and persistence. IFN-gamma has been shown to activate the JAK-STAT pathway in keratinocytes. Previous reports have demonstrated efficacy of Janus kinase (JAK) inhibitors in lichen

planopilaris, nail LP, and recently in 3 patients with oral ELP. A recent review summarizes the cases of LP where 3 JAK inhibitors were used with success: tofacitinib, baricitinib, and upadacitinib. Here, we report a case series of 6 patients with a diagnosis of EVVLP who were treated with oral tofacitinib.

Hybrid cooperative complexes to decrease VAS score and enhance sexual function in women with vulvar lichen sclerosus

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Objective: Lichen sclerosus is a chronic, inflammatory, progressive skin disease predominantly affecting anogenital areas. Vulvar lichen sclerosus (VLS) is one of the most common conditions treated in vulvar clinics; most patients report distressing symptoms of itching, burning, stinging, and pain (particularly during or after sexual intercourse). A preliminary, prospective, single-center study was performed to investigate the efficacy of hyaluronan hybrid cooperative complex (HCC) comprising high and low molecular weight hyaluronic acid to treat menopausal women with VLS. **Patients and methods:** Patients (N = 30) received two HCC injections at 32 mg/ml (one month apart). At baseline and one and six months after treatment, patients completed validated psychometric questionnaires to assess their self-reported pain, itching, and dryness using the Visual Analogue Scale (VAS) and sexual function by the Female Sexual Function Index (FSFI). **Results:** After treatment with HCC, no side effects or complications were reported. VAS scores showed a trend towards reduced pain and itching intensity, and there was a statistically significant reduction in median VAS score for dryness at follow-up vs. baseline (p=0.038). For sexual function, there was a statistically significant improvement in lubrication (p=0.001) and orgasm (p=0.001) FSFI domains. **Conclusions:** Overall, this preliminary study demonstrated the promising efficacy of HCC in menopausal women with VLS without side effects.

Application of clitoris exposure + episioplasty + dermabrasion + platelet-rich plasma injection + chemexfoliation in vulvar lichen sclerosus

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Introduction: To investigate the therapeutic effect of clitoris exposure + episioplasty + dermabrasion + platelet-rich plasma (PRP) injection + chemexfoliation on vulvar lichen sclerosus (VLS). **Methods:** Twenty children with VLS (under 14 years old) at our hospital from July 2020 to November 2022 were enrolled and treated with clitoris exposure + episioplasty + dermabrasion + PRP injection + chemexfoliation. Additionally, symptomatic changes and improvements in signs were recorded. **Results:** Significant therapeutic effects were achieved in all children enrolled in this study. The Cattanco score was 8.02 ± 1.22 points before surgery, 2.21 ± 0.70 points 3 months after surgery, and 2.61 ± 0.59 points 6 months after surgery, demonstrating that the score after surgery was significantly lower than that before surgery ($p < 0.05$). Mild complications (one case of mild vulvar swelling, one case of minor bleeding, and one case of superficial ulcer) were observed in three children after surgery, with an overall complication incidence of 15%; all complications were improved after the intervention, and no severe adverse reactions were observed. Recurrence was observed in one child (5%) 6 months after surgery. **Conclusion:** Clitoris exposure + episioplasty + dermabrasion + PRP injection + chemexfoliation is an effective approach for the treatment of VLS.

Prevalence of prescribing topical corticosteroids to patients with lichen sclerosus following surgery for vulvar cancer: a survey among gynaecologic oncologists in The Netherlands

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Background: Vulvar lichen sclerosus (LS) is a chronic inflammatory dermatosis which can progress to precursor lesion differentiated vulvar intraepithelial neoplasia (dVIN) and vulvar squamous cell carcinoma (VSCC). The risk of developing recurrent vulvar cancer following LS-associated VSCC is high. Evidence suggests that treatment of LS with topical corticosteroids (TCS) can prevent progression to dVIN, VSCC and recurrences. However, current guidelines do not give any recommendation on the management of LS following surgery for VSCC. The aim of this study was to conduct a survey among all registered gynaecologic oncologists (GOs) in the Netherlands to evaluate the current management of LS patients without a history of VSCC (LS^{noVSCC}) and patients with LS following surgery for VSCC (LS^{VSCC}).
Methods: An online survey was distributed to all registered GOs in the Netherlands. Primary outcome measures were the frequency, type and duration of TCS treatment prescribed for LS^{noVSCC} and LS^{VSCC} patients, separately. As a secondary outcome measure, reasons for treating or not treating patients with LS^{noVSCC} and LS^{VSCC} with TCS were analysed. **Results:** Forty-four GOs completed the survey, resulting in a response rate of 75%. TCS were prescribed more often to patients with LS^{noVSCC} as compared to patients with LS^{VSCC} (86% *versus* 52%, respectively, $p < 0.001$). If treatment was initiated, ultra-potent (class IV) TCS were most commonly prescribed for an indefinite period of time for both patient groups. The most reported reason for treating patients in both groups with TCS was symptoms, followed by clinical aspects of the lesion and prevention of progression to dVIN and VSCC.
Conclusion: The majority of GOs who participated in our study endorse the utilisation of long-term ultra-potent TCS therapy in both patients with LS^{noVSCC} and LS^{VSCC}. Nevertheless, Dutch GOs are currently prescribing TCS more frequently to patients with LS^{noVSCC} than to patients with LS^{VSCC}.